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PREPARATION METHOD OF 2-AMINO- AND 2-(DISUBSTITUTED AMINO)-4,5-DIARYLIMIDAZOLES

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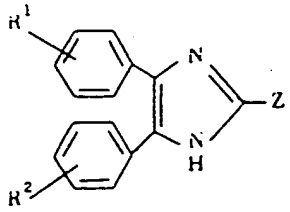
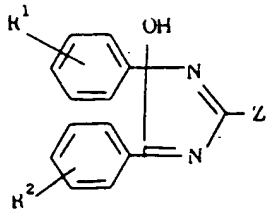
[Attached amendments have been incorporated into text of translation.]

Claim

A preparation method of 2-amino- and 2-(disubstituted amino)-4,5-diarylimidazoles having the following formula (I)

(I) 

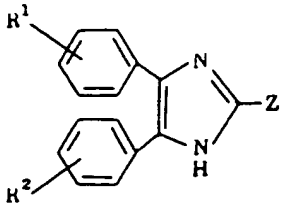
(in the formula, R_1 and R_2 are hydrogen, alkyl, alkoxy, or halogen; Z is amino, N,N-dialkylamino, N-alkyl-N-aralkylamino, N,N-diaralkyl, pyrrolidino, piperidino, N-alkylpiperidino or morpholino), characterized by catalytically reducing 4-hydroxy-4H-imidazoles having the following formula (II)

(II) 

(in the formula, R_1, R_2, and Z are the same as above).

Detailed explanation of the invention

The present invention relates to a preparation method of imidazole derivatives of compounds having the formula (I)

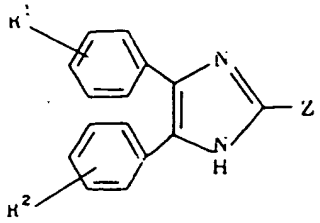
(I) 

(in the formula, R_1 and R_2 are hydrogen, alkyl, alkoxy, or halogen; Z is amino, N,N-dialkylamino, N-alkyl-N-aralkylamino, pyrrolidino, piperidino, N-alkylpiperidino or morpholino).

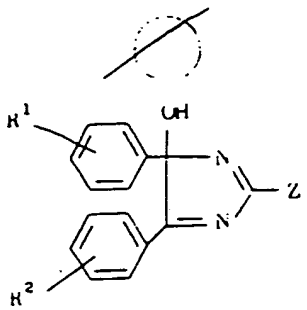
Some of the 2-amino-4,5-diarylimidazoles to be obtained by the present invention are prepared by reacting α-aminocarbonyl compounds with cyanamides (G.C. Lancini and E. Lazzari, J. Heterocyclic Chem., 3, 152 (1966)) or by reduction of 2,2'-azoimidazole (A.

Kreutzberger, J. Org. Chem., 27, 886 (1962)), but those methods have drawbacks of difficulty in obtaining raw materials or poor yield of desired products.

It was found in this invention that 2-amino- and 2-(disubstituted amino)-4,5-diarylimidazoles having the formula (I)

(I) 

are obtained at high yield by catalytically reducing 4-hydroxy-4H-imidazoles having the formula (II)

(II) 

(in the formula, R_1, R_2, and Z are same as above), and the present invention was completed.

Generally, alcohols are difficult to reduce, and easy catalytic reduction of 4-hydroxy-4H-imidazoles is an absolutely unexpected result. Among compounds of the formula (I), especially 2-(disubstituted amino)-4,5-diarylimidazoles are new compounds not found in the literature, and those compounds could be synthesized by the present invention for the first time.

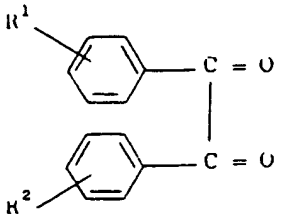
In the application of this invention method, the compounds of formula (II), or their salts, are hydrogenated in a suitable organic solvent, e.g., alcohols, halogenated hydrocarbons, esters, preferably methanol, in the presence of a suitable catalyst, e.g., platinum oxide, palladium carbon/Raney nickel, at -10°C-40°C and preferably 0°C to 25°C for 3-48 h to obtain the desired compounds. The amount of the catalyst is preferably 1/20 to 1/3 of the starting materials (II). After completing the reduction, the catalyst is removed by filtering to separate the desired product as a free base, but it is convenient to separate it as an acid salt by adding a suitable mineral acid to the reaction mixture and allowing it to stand, or naturally cooling after concentrating, or concentrating it to a solid and recrystallizing it from a suitable solvent such as methanol, ethanol, i-propanol, n-butanol, or mixed solvents of alcohol and ether, and hydrochloride salt and nitrate salt are especially suitable for this purpose. The 2-aminoimidazole derivatives obtained by this invention method are useful as intermediates for the preparation of nitroimidazoles having antitrichomonas activity, and the 2-aminoimidazole derivatives and the

2-disubstituted aminoimidazole derivatives have antibacterial activity and other biological activities.

In the aforementioned synthetic method of Lancini et al., α-aminocarbonyl compounds as general raw materials are unstable and difficult to handle. Especially, the synthesis of α-aminoaldehyde is difficult; the yield is bad; in addition, various by-products are easily formed according to pH of the reaction solution and thus, the yield is generally low. Furthermore, in the aforementioned synthetic method of Kreutzberger et al., the yield of desired products is satisfactory, but it is necessary to use aminoguanidine for preparation of biguanide, which is used as raw material; further, the yield is extremely low. Thus, the present invention method of reducing 4H-imidazoles, which are prepared at a high yield from guanidines as raw materials, is superior to known method, in addition, 2-disubstituted aminoimidazoles can be prepared only by this invention method.

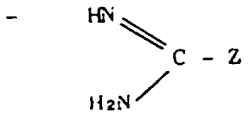
Furthermore, 4-hydroxy-4H-imidazoles of formula (II), which are used as raw materials in this invention, are new compounds and can be prepared by reacting substituted or unsubstituted benzyl having formula (III)

(III)



(in the formula, R^1 and R^2 are same as above)
with guanidine derivatives having the following formula (IV)

(IV)



(in the formula, Z is same as above)
in a suitable organic solvent such as lower alkanol, e.g., methanol (refer to Japanese Patent Application No. Sho 52[1977]-103181 applied by present inventor at the same date (Title of Invention: 4-Hydroxy-4,5-diaryl-4H-imidazoles and manufacturing method thereof)).

Next, this invention's method will be explained by application examples.

Application Example 1 Preparation of 2-amino-4,5-diphenylimidazole

2.77 g 2-amino-4-hydroxy-4,5-diphenyl-4H-imidazole and 0.60 g 5% palladium carbon were suspended in 20 mL methanol, and hydrogen was added at room temperature. When the

absorption of hydrogen gas stopped, the catalyst was removed by natural filtration, and the filtrate was concentrated and dried to a solid, and then a small amount of methanol was added to the residue and allowed to stand at room temperature. The formed crystal was collected by filtering, washed with a small amount of ethanol, and air-dried to obtain a lemon-yellow columnar crystal.

Yield: 1.97 g (84%), Melting point 231-235°C (decomposed). It was recrystallized from ethanol to obtain a product with melting point of 233-235°C (literature value 233-234°C (decomposed)).

Application Example 2 Preparation of 2-amino-4,5-diphenylimidazole nitrate

After reacting in the same manner as that in Application Example 1, the catalyst was removed by filtering, and nitric acid of a calculated amount was added to the filtrate. After allowing to stand for one night, the precipitate was collected by filtering, washed with a small amount of methanol, and air-dried to obtain nitrate and colorless acicular crystal. Melting point 163-164°C (decomposed), Yield 1.94 g. The filtrate was concentrated to about 5 mL, and 40 mL ether were added and allowed to stand to obtain nitrate again. Melting point 159-161°C. Yield 0.64 g. Total yield 2.58 g (88%). When crystallized from methanol, a colorless acicular crystal with a melting point of 167°C (decomposed) was obtained.

Elemental analysis (with respect to $C_{15}H_{13}N_3 \cdot HNO_3$)

Calculated value: C 60.39, H 4.73, N 18.78%

Measured value: C 60.34, H 4.78, N 19.07%

Application Example 3 Preparation of 2-amino-4,5-di(p-chlorophenyl)imidazole hydrochloride

1.60 g 2-amino-4-hydroxy-4,5-di(p-chlorophenyl)-4H-imidazole and 0.40 g 5% palladium carbon were suspended in 30 mL methanol, and hydrogen was added at room temperature. After completing the reaction, 0.7 mL concentrated hydrochloric acid was added to the reaction solution and filtered to remove the catalyst, and the filtrate was concentrated, dried to a solid, and then the residue was vacuum-dried in a desiccator for one day to obtain a white powder. Yield 1.62% (95%). Melting point 111°C (partially foamed), 238°C (decomposed). When recrystallized from ethanol and ether, a colorless acicular crystal was obtained. Melting point 268-269°C (decomposed).

Elemental analysis (with respect to $C_{15}H_{11}N_3Cl_2 \cdot HCl$)

Calculated value: C 52.89, H 3.55, N 12.33%

Measured value: C 52.85, H 3.85, N 12.57%

Application Example 4 Preparation of 2-amino-4,5-di(p-chlorophenyl) imidazole nitrate

The same reaction as that in Application Example 3 was carried out. But after the catalyst was removed by filtering, a calculated amount of nitric acid, instead of concentrated hydrochloric acid, was added. The reaction solution was concentrated to about 5 mL, and 2 mL ethanol were added and kept cold to obtain a white acicular crystal. Yield 1.27 g (70%), Melting point 157-9°C (decomposed). It was recrystallized from ethanol to obtain a colorless columnar crystal. Melting point 160°C (decomposed).

Elemental analysis (with respect to $C_{15}H_{11}N_3 \cdot HNO_3$)

Calculated value: C 49.06, H 3.29, N 15.26%

Measured value: C 49.08, H 3.33, N 15.25%

Application Example 5 Preparation of 2-amino-4,5-di(p-methylphenyl)imidazole hydrochloride

3.11 g 2-amino-4-hydroxy-4,5-di(p-methylphenyl)-4H-imidazole and 1.20 g 5% palladium carbon were suspended in 50 mL methanol, hydrogenated at room temperature, and filtered in a hot state after adding 1.4 mL concentrated hydrochloric acid, and the filtrate was concentrated and dried to a solid. The residue was dissolved in 6 mL hot methanol and naturally cooled at room temperature. The produced crystal was collected by filtering, washed once with 3 mL methanol, and air-dried to obtain a lemon-yellow columnar crystal. Melting point 244-255°C (decomposed), Yield 2.40 g (78%). It was recrystallized from methanol to obtain a lemon-yellow columnar crystal. Melting point 255-259°C (decomposed).

Elemental analysis (with respect to $C_{17}H_{17}N_3 \cdot HCl\ 1/2H_2O$)

Calculated value: C 66.12, H 6.20, N 13.60%

Measured value: C 66.23, H 6.18, N 13.71%

Application Example 6 Preparation of 2-amino-4,5-di(p-methylphenyl)-imidazole nitrate

The same reaction as that in Application Example 5 was carried out. But after removing the catalyst by filtering a calculated amount of, nitric acid, instead of concentrated hydrochloric acid, was added. The reaction solution was filtered in a hot state, and the filtrate was concentrated to about 5 mL and kept cold to obtain a light yellowish-green granular crystal. Melting point 202°C (decomposed), Yield 3.04 g (93%). It was recrystallized from ethanol to obtain a light-yellow columnar crystal. Melting point 186°C (decomposed).

Elemental analysis (with respect to $C_{17}H_{17}N_3 \cdot HNO_3$)

Calculated value: C 62.56, H 5.56, N 17.17%

Measured value: C 62.62, H 5.63, N 17.19%

Application Example 7 Preparation of 2-dimethylamino-4,5-diphenylimidazole hydrochloride

1.40 g 2-methylamino-4-hydroxy-4,5-diphenyl-4H-imidazole were hydrogenated in 150 mL methanol containing 0.15 g platinum oxide, and after completing the reaction, 0.7 mL concentrated hydrochloric acid was added to the reaction solution. The catalyst was removed by filtering and the filtrate was concentrated and dried to a solid. The residue was dissolved in 27 mL hot methanol and filtered in a hot state, and the filtrate was naturally cooled to room temperature. The precipitated crystal was collected by filtering and air-dried to obtain a colorless columnar crystal with melting point 261-271°C (decomposed). Yield 0.76 g. The mother liquor after removing the crystal was similarly treated to obtain a colorless columnar crystal with melting point 278-283°C (decomposed) at a yield of 0.32 g. Total yield 1.08 g (72%). It was recrystallized from ethanol to obtain a colorless columnar crystal. Melting point 283°C (decomposed).

Elemental analysis (with respect to $C_{17}H_{17}N_3 \cdot HCl$)

Calculated value: C 68.11, H 6.05, N 14.02%

Measured value: C 68.06, H 6.26, N 14.07%

Application Example 8 Preparation of 2-dimethylamino-4,5-di(p-methoxyphenyl)imidazole hydrochloride

1.69 g 2-methylamino-4-hydroxy-4,5-di(p-methoxyphenyl)-4H-imidazole and 0.17 g platinum oxide were reacted in 150 mL methanol by the same manner as that in Application Example 7. Yield 1.46 g (82%), Melting point 238-241°C (decomposed).

It was recrystallized from ethanol to obtain a colorless acicular crystal. Melting point 239-241°C (decomposed).

Elemental analysis (with respect to $C_{19}H_{21}N_3O_2 \cdot HCl$)

Calculated value: C 63.42, H 6.16, N 11.68%

Measured value: C 63.44, H 6.42, N 11.92%

Application Example 9 Preparation of 2-dimethylamino-4,5-di(p-chlorophenyl)imidazole hydrochloride

1.39 g 2-dimethylamino-4-hydroxy-4,5-di(p-chlorophenyl)-4H-imidazole were hydrogenated in 150 mL methanol containing 0.14 g platinum oxide, and after completing the reaction, 0.5 mL concentrated hydrochloric acid was added. The catalyst was removed by filtering, and the filtrate was concentrated and dried to a solid. The residue was dissolved in 26 mL hot methanol and filtered in a hot state, and the filtrate was naturally cooled. The produced crystal was collected by filtering and air-dried to obtain a colorless granular crystal with melting point of 303°C or higher and a yield of 0.57 g. When 22 mL ether were added to the

filtrate, a colorless granular crystal with melting point of 303°C or higher was obtained at a yield of 0.41 g. Total yield 0.98 g (66%)
Mass spectra: m/e 331 (M^+, 100%)

Application Example 10 Preparation of 2-(N-benzyl-N-methylamino)-4,5-diphenylimidazole hydrochloride

0.35 g 2-(N-benzyl-N-methylamino)-4-hydroxy-4,5-diphenyl-4H-imidazole and 0.04 g platinum oxide were treated by the same manner as that in Application Example 7. Yield 100%. It was recrystallized from ethanol to obtain a colorless acicular crystal. Melting point 228-232°C (decomposed)
Mass spectra: m/e 339 (M^+, 91%)

Application Example 11 Preparation of 2-pyrrolidino-4,5-di(p-methoxyphenyl)-imidazole hydrochloride

1.48 g 2-pyrrolidino-4-hydroxy-4,5-di(p-methoxyphenyl)-4H-imidazole and 0.15 g platinum oxide were suspended in 40 mL methanol and treated by the same manner as that in Application Example 7 to obtain a white granular crystal. Melting point 268-271°C (foamed), Yield 1.21 g (79%). When it was recrystallized from ethanol and ether, the melting point was 269-271°C.
Elemental analysis (with respect to $C_{21}H_{33}N_3O_2 \cdot HCl$)
Calculated value: C 65.36, H 6.27, N 10.89%
Measured value: C 65.49, H 6.27, N 10.90%

Application Example 12 2-(N-benzyl-N-methylamino)-4,5-di(p-methoxyphenyl)imidazole hydrochloride

0.45 g 2-(N-benzyl-N-methylamino)-4-hydroxy-4,5-di(p-methoxyphenyl)-4H-imidazole hydrochloride was hydrogenated in 10 mL methanol containing 0.05 g platinum oxide at room temperature. After completing the reaction, the catalyst was removed by filtering, and the filtrate was concentrated, dried to a solid, and vacuum-dried. Yield 100%. It was recrystallized from ethanol and ether to obtain a light green plate-form crystal. Melting point 234-238°C (decomposed).
Mass spectra: m/e 399 (M^+, 100%)

Application Example 13 Preparation of 2-(N-methylpiperidino)-4,5-diphenylimidazole hydrochloride

3.34 g 2-(N-methylpiperadino)-4-hydroxy-4,5-diphenyl-4H-imidazole and 0.33 g platinum oxide were treated in 100 mL methanol by the same manner as that in Application Example 7 to obtain a white powder. Melting point 268°C (decomposed), Yield 3.43 g (97%). It was recrystallized from ethanol to obtain a pink acicular crystal. Melting point 281°C (decomposed).

Mass spectra: m/e 319 (M^+, 100%).